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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
CLARK, SARA E	
ART UNIT	PAPER NUMBER
1613	

NOTIFICATION DATE	DELIVERY MODE
09/01/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/594,160	RASMUSSEN ET AL.	
	Examiner	Art Unit	
	SARA E. CLARK	1613	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 April 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-25* is/are pending in the application.

4a) Of the above claim(s) *1,2 and 15-25* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *3-14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1/12/2010 and 4/16/2010*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

NON-FINAL REJECTION

Receipt is acknowledged of Applicants' Amendments and Remarks, filed 4/16/2010.

Claims 1-25 are pending.

No new claims have been added.

Claims 1, 2, and 15-25 are withdrawn as being drawn to a nonelected invention.

Claims 3, 4, 8, 9, 12, and 13 have been amended and incorporate no new matter.

Thus, claims 3-14 now represent all claims currently pending and under consideration.

REQUEST FOR CONTINUED EXAMINATION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 4/16/2010 has been entered.

FORMALITIES

Claim 8 contains a misspelling:

"β_3-drenoceptor" should be corrected to "β_3-adrenoceptor."

INFORMATION DISCLOSURE STATEMENT

The information disclosure statements (IDS) submitted on 1/12/2010 and

4/16/2010 are in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statements have been considered by the examiner.

WITHDRAWN REJECTIONS

Rejections under 35 USC §112

Due to the amendments to the claims, the rejection of claim 8 under 35 USC 112, second paragraph, for indefiniteness, is withdrawn.

Rejections under 35 USC §103(a)

Due to the amendments to the claims, the rejection of claims 3-5 and 9-12 under 35 USC 103 as obvious over Carson and Wheeldon is withdrawn.

Due to the amendments to the claims, the rejection of claims 6-8 under 35 USC 103 as obvious over Carson and Wheeldon, further in view of Gauthier, is withdrawn.

Due to the amendments to the claims, the rejection of claims 13 and 14 under 35 USC 103 as obvious over Carson and Wheeldon, further in view of Cecil, is withdrawn.

NEW REJECTIONS

Claim Rejections - 35 USC § 112, Second Paragraph

1. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims 3-14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, the claims recite methods of treating a population of patients "susceptible to heart failure or myocardial hypertrophy." However, the specification does not define "susceptible" so as to clearly circumscribe the patient population encompassed, and this term does not have a commonly understood and accepted meaning in the art. Because infringing activity cannot be clearly distinguished from non-infringing activity, the metes and bounds of the claims are indefinite.

Claim Rejections - 35 USC § 112, First Paragraph

Written Description

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 3-14 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Specifically, the claims recite methods of treating a human "susceptible to heart failure or myocardial hypertrophy." However, the specification does not define

"susceptible" so as to clearly circumscribe the patient population encompassed, describe how "susceptible" patients can be identified, or set forth criteria for distinguishing patients who are susceptible to heart failure from patients who are not susceptible to heart failure. The only guidance given in the specification is within the definition of "heart failure," which includes "symptomatic heart failure and asymptomatic heart failure, and therefore includes susceptibility to acute or chronic heart failure" (p. 8, lines 1-6).

The purpose of the written description requirement is to ensure that the inventor had possession of the specific subject matter claimed as of the filing date of the application. As recognized by MPEP §2163:

> "To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that the inventor invented the claimed invention." *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997); *In re Gostelli*, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) ("[T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed"). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." *Lockwood*, 107 F.3d at 1572, 41 USPQ2d at 1966." *Regents of the University of California v. Eli Lilly & Co.*, 43 USPQ2d 1398.

The written description requirement of 35 U.S.C. §112 requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See *In re Wilder*, 736, F.2d 1516, 1521, 222 USPQ 369, 372-73 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin[e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate.") Accordingly, it is deemed that the specification fails to provide

adequate written description of the population of patients "susceptible to heart failure or myocardial hypertrophy," and does not reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the entire scope of the claimed invention.

Enablement

5. Claims 3-14 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. MPEP §2164.01(a), citing *In re Wands,* 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), sets out the factors to determine whether experimentation is undue, which include:

(A) The breadth of the claims. Claims 3-14 are drawn to methods of treating a human suffering from or susceptible to heart failure or myocardial hypertrophy, comprising administering a therapeutically effective amount of one or more β_3 adrenoceptor agonists.

Heart failure is a condition in which the heart can no longer pump enough blood to the rest of the body. It is almost always a chronic, long-term condition, although it can sometimes develop suddenly; and it may affect the right side, the left side, or both sides of the heart (see MedlinePlus, 2009). The specification defines "heart failure" (HF) to

include both chronic and acute heart failure; both symptomatic and asymptomatic heart failure; and both systolic and diastolic heart failure (p. 7, line 34 to p. 8, line 6).

Further, the European Society of Cardiology (ESC) Guidelines (provided by Applicant on the IDS dated 4/16/2010) define heart failure as a syndrome characterized by the following features: symptoms of HF, typically shortness of breath at rest or during exertion, and/or fatigue; signs of fluid retention such as pulmonary congestion or ankle swelling; and objective evidence of an abnormality of the structure or function of the heart at rest" (ESC Guidelines, p. 935, right column; Table 3). Thus, the claims encompass any and all stages of heart failure, a broadly defined condition which may not always be readily identifiable.

(B) The nature of the invention. It was known in the art that β_1-, β_2-, and β_3-adrenoceptors are activated by endogenous catecholamines, such as epinephrine and norepinephrine, albeit in varying concentrations (see, e.g., Gauthier et al. TiPS 2000, abstract, cited in the previous Office Action). It was also well-known to administer β_1- and β_2-adrenoceptor antagonists (a.k.a. "β-blockers") as a pharmacological therapy to treat heart failure (see, e.g., ESC Guidelines, pp. 951-952). In contrast, the claimed invention is drawn to the administration of one or more agonists of the β_3 adrenoceptor.

(C) The state of the prior art and level of predictability in the art. Moniotte et al. (Intensivmed 2003, p. 485) and Gauthier et al. (TiPS 2000, pp. 426-427) disclose BRL 37344 as a β_3-adrenoceptor agonist, and nadolol as a β_1-/β_2-adrenoceptor antagonist, in human cardiac tissue.

Moniotte et al. disclose that activation of β-adrenoceptors had been exclusively associated with stimulation of cardiac contraction. However, contrary to β_1- and β_2-adrenoceptor pathways, activation of the β_3-adrenoceptor, either by norepinephrine or the selective β_3 agonist BRL 37344, decreases contractile force (p. 485, para. bridging left and right columns). BRL 37344 also elicits a negative inotropic effect in the presence or absence of β_1-/β_2 blockade with nadolol (p. 485, right column).

Applicant explains that a negative inotropic response (i.e., a decrease in contractility) would not be considered desirable at any stage of heart failure; rather, this would be harmful (Remarks dated 4/16/2010, para. bridging pp. 11-12). Hence, administration of a β_3 agonist to a human with heart failure would be expected to decrease the contractility of the already failing heart, thereby exacerbating the condition rather than treating it (Remarks, p. 9).

In addition, Stamler et al. (US Pub. 2004/0053852, provided by applicant on the IDS dated 1/12/2010, disclose that "[i]t is known that in chronic heart failure, catechol-amines are highly elevated and thus the [β-adrenergic] receptor may be down-regulated and/or the system desensitized, and that β-adrenergic agonists and other inotropic agents can kill patients, if used chronically because of further down-regulation and desensitization" (para. 0025).

Gauthier et al. (TiPS 2000) disclose that in the failing heart, β_1- and β_2-adrenoceptors are either downregulated or desensitized, while the abundance of β_3-adrenoceptors appears to increase. Gauthier et al. propose that this compensatory upregulation of the β_3-adrenoceptor could be viewed as a mechanism to prevent further

myocyte damage; however, as heart failure progresses to a later stage, this compensatory mechanism may become maladaptive, with a persistent negative inotropic effect leading to further myocardial depression (p. 430, left column).

Moniotte et al. reinforce this, pointing out that "the β_3 adrenoceptor pathway would function as a countervailing 'rescue' mechanism preventing myocyte damage from excessive stimulation of β_1- and β_2-adrenoceptors. However, as myocardial depression progress to a later stage, this compensatory mechanism might be maladaptive, with a persistent negative inotropic effect leading to further myocardial dysfunction" (p. 490, para. bridging left and right columns). While Moniotte et al. point out that β_3 adrenoceptor stimulation may not be uniformly deleterious (p. 490, right column), Gauthier et al. disclose that, at this later stage, β_3 adrenoceptor antagonists might be more desirable" (TiPS 2000, p. 430, right column).

Addressing Gauthier et al. (TiPS 2000), Applicant states that (Remarks, p. 12; emphasis added):

> Gauthier's hypothesis that choice of β blockers could be based on the effects of β_3 adrenoceptor-mediated pathways at different stages of disease would have been recognized by the skilled addressee as **profoundly flawed.** Central to the prospect of any therapeutic benefit arising from that hypothesis is **the ability of the treating physician to clearly distinguish different stages of heart failure. Even now that is not easily achieved.** In support of that opinion, the Examiner is referred to the European Society of Cardiology (ESC) Guidelines which indicate that the definition and diagnosis of heart failure is not straightforward (see for example, pages 935-937 of the ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2008; European Journal of Heart Failure (2008), 933-989) . . .
>
> As a result there is no practical way that any transition from "early stages" to "later stages" of heart failure, as would be required under Gauthier's hypothetical approach, can be reliably identified. As is widely recognized by clinicians, such a transition can be gradual and insidious or there can be rapid decompensation for no apparent reason. **Without an ability to reliably detect the stage when a β_3 receptor agonist would be harmful in heart failure, such an agonist would not be considered safe and so would never be approved by regulatory authorities (e.g. FDA) for use in heart failure at any stage.**

Thus, while there is evidence that β_3 adrenoceptor stimulation in the failing heart could be beneficial (e.g., in earlier stages) or detrimental (e.g., in later stages), there is also evidence that these earlier and later stages of HF cannot be readily distinguished, such that a treating physician could not reliably predict when the administration of a β_3 agonist would be helpful or harmful. Because the prior art discloses embodiments falling within the scope of the claims that would be likely to exacerbate rather than treat the claimed conditions (e.g., administration of a β_3 agonist after myocardial depression has progressed to a later stage), the art must be regarded as highly unpredictable.

(D) The amount of direction provided and/or the existence of working examples. The specification presents data from six experiments. Examples 1-5 describe the use of the whole-cell patch-clamp technique to measure the effect of the β_3 agonist BRL 37344 on rabbit cardiac myocytes, at concentrations of 1, 10, and 100 nM. These examples conclude with the following: "[t]aken together, the results presented here indicate that activation of β_1/β_2-adrenergic receptors cause Na+-K+ pump inhibition, while activation of β_3 adrenergic receptors cause Na+-K+ pump stimulation," which is "expected to promote Na+ export from Na+ overloaded cells in heart failure, thereby providing a beneficial therapeutic effect" (specification p. 27, lines 29-35).

Example 6 describes the effect of the β_3 agonist BRL 37344 in a sheep model of severe heart failure induced by repeated coronary microembolization. Because BRL 37344 was found to effect a dose-dependent improvement in left ventricular function, "[i]t is concluded that β_3 adrenergic receptors activation has acute beneficial effects in heart failure."

The working examples do not include any data relating to human cardiac tissue. As noted in the previous Office Action, it was well-known that β_3 adrenoceptor expression, as well as the cardiac effects of β_3 agonists, show substantial variability among mammalian species (see, e.g., Gauthier et al., TiPS 2000, p. 427; and Gauthier et al., Can. J. Physiol. Pharmacol. 2000, pp. 683-84, both cited in the Office Action dated 10/16/2009). Supporting this position, Applicant has cited Arch 2002, which discloses that the challenge of identifying agonists selective for the β_3 adrenoceptor in human tissue is compounded by differences in pharmacology between the rodent and human β_3 adrenoceptors (Remarks, p. 8). Species have been classified by myocardial response to β_3 agonist stimulation: hyper-responders (human and dog), hypo-responders (rat and guinea pig) and non-responders (ferret) (see Gauthier et al., Can. J. Physiol. Pharmacol. 2000, p. 684). Rabbits and sheep are not classified. Thus, a skilled artisan would not necessarily extrapolate results obtained in other mammalian species to human cardiac tissue.

Further, Pott et al. (Br. J. Pharm. 2003) disclose that "[i]n human left ventricular myocardium, BRL [37344] and other β_3-AR [adrenoceptor] agonists have been described to decrease FOC (force of contraction) via the β_3-AR" (p. 521, para. bridging left and right columns). As noted by applicant, a decrease in contractility would be harmful in heart failure (Remarks, para. bridging pp. 11-12). However, Pott et al. disclose that, in human right atrial tissue taken from patients with coronary heart disease or valvular disease, BRL 37344 increases FOC in a concentration-dependent manner (Fig. 2b), and does not directly induce negative inotropic effects as it does in

the left ventricle (p. 527, right column). Thus, β_3 agonist stimulation with BRL 37344 appears to have conflicting effects in human cardiac tissue, decreasing contractility in the left ventricle while increasing contractility in the right atrium.

Finally, the prior art suggests that β_3 inhibition may have a beneficial effect in later stages of heart failure (see, e.g., Gauthier et al., TiPS 2000, p. 430, right column), which in turn suggests that a β_3 agonist would be harmful or might aggravate the condition, or that β_3 antagonism would be preferable. In contrast, other references suggest that β_3 stimulation may have a beneficial effect in later stages of heart failure: by increasing nitric oxide synthesis, additional vasodilating effects on vessel tone "might also contribute to decrease the peripheral vascular resistance and the afterload of the failing heart. Also, a local nitric oxide release in the myocardium . . . could enhance diastolic relaxation and reduce oxygen consumption, thereby improving cardiac status" (Moniotte, p. 490, right column).

Thus, the working examples presented in the specification do not resolve the conflicting and contradictory data known in the prior art, so as to enable one skilled in the art to treat heart failure or myocardial hypertrophy in humans by administering one or more β_3 adrenoceptor agonists.

(E) The quantity of experimentation needed to make or use the invention. The data presented in the specification supports a link between β_3 stimulation with BRL 37344 and stimulation of the Na+/K+ pump, and the administration of BRL 37344 to improve left ventricular function in a sheep model. However, in view of the species variations and significant unpredictability in the art, coupled with a lack of guidance and

direction provided by the instant disclosure, a skilled artisan would be required to conduct much more than routine experimentation in order to bridge the gap between the disclosure and a working embodiment which could reasonably be expected to treat a human suffering from or susceptible to heart failure or myocardial hypertrophy.

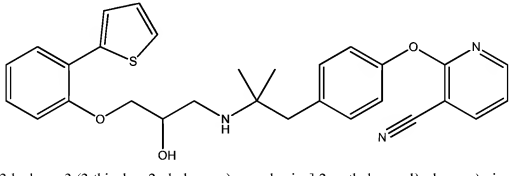
Claim Rejections - 35 USC § 102

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7. Claims 3 and 5 are rejected under 35 U.S.C. 102(b) as being anticipated by Bush et al. (WO02/94820, provided by Applicant on the IDS dated 1/12/2010).

Bush et al. disclose methods of administering a β_3 adrenoceptor agonist, in particular 2-(4-{2-[2-hydroxy-3-(2-thiophen-2-yl-phenoxy)-propylamino]-2-methyl-propyl}-phenoxy)-nicotinonitrile (SAM II),



2-(4-{2-[2-hydroxy-3-(2-thiophen-2-yl-phenoxy)-propylamino]-2-methyl-propyl}-phenoxy)-nicotinonitrile

to treat diseases in humans, including congestive heart failure (abstract; p. 25, lines 2-25), as recited by claim 3.

Because the core structure of SAM II is an aryloxypropanolamine, this compound falls within the scope of the term aryloxypropanolamine, as recited by claim 5.

Thus, Bush et al. anticipates claims 3 and 5.

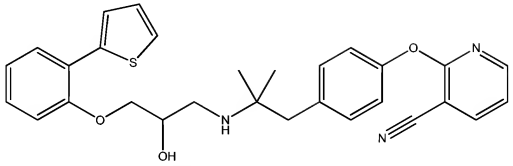
Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. Claims 3 and 5-12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bush et al. (WO02/94820, provided by Applicant on the IDS dated 1/12/2010), in view of Moniotte et al. (Intensivmed 40, 484-493, 2003) and the European Society of Cardiology (ESC) Guidelines (provided by Applicant on the IDS dated 4/16/2010).

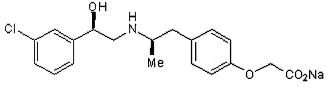
Bush et al. disclose methods of administering a β_3 adrenoceptor agonist, in particular 2-(4-{2-[2-hydroxy-3-(2-thiophen-2-yl-phenoxy)-propylamino]-2-methyl-propyl}-phenoxy)-nicotinonitrile (SAM II),



2-(4-{2-[2-hydroxy-3-(2-thiophen-2-yl-phenoxy)-propylamino]-2-methyl-propyl}-phenoxy)-nicotinonitrile

to treat diseases in humans, including congestive heart failure (abstract; p. 25, lines 2-25), as recited by claim 3.

Moniotte et al. disclose that BRL 37344, is a β_3-adrenoceptor agonist in human cardiac tissue (p. 485), as recited by claims 6 and 7. The structure of BRL 37344,



has an arylethanolamine core; thus, this compound falls within the scope of the term arylethanolamine, as recited by claim 5.

While Moniotte et al. does not explicitly disclose that BRL 37344 also has β_1- or β_2-adrenoceptor antagonist activity, as recited by claim 8, this is an inherent property of the compound. As recognized by MPEP §2112, the claiming of a new *property* which was inherently present in the prior art composition at all times does not distinguish it over the prior art. *In re Best*, 562 F.2d 1252, 1254, 195 USPQ 430,433 (CCPA 1977). There is no requirement that a person of ordinary skill in the art would have recognized the inherent disclosure at the time of invention, but only that the subject matter is in fact

inherent in the prior art reference. *Schering Corp. v. Geneva Pharm. Inc.* 339 F.3d 1373, 1377, 67 USPQ2d 1664, 1668 (Fed. Cir. 2003).

Moniotte et al. also disclose nadolol as a β_1-/β_2-adrenoceptor antagonist, and the simultaneous co-administration of BRL 37344 and nadolol (p. 485), as recited by claims 9-12. As disclosed by the ESC Guidelines, it was known in the art to administer β_1- and/or β_2-adrenoceptor antagonists (a.k.a. "β-blockers") as a pharmacological therapy to treat heart failure.

Because the references disclose the treatment of heart failure in humans by administering a β_3 adrenoceptor agonist, and/or a β_1-/β_2-adrenoceptor antagonist, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to modify the method of Bush et al. by substituting the human β_3-adrenoceptor agonist SAM II with the human β_3-adrenoceptor agonist BRL 37344, as taught by Moniotte et al., and to co-administer a human β_1-/β_2-adrenoceptor antagonist such as nadolol, as taught by the ESC Guidelines, with a reasonable expectation of success. As recognized by MPEP §2144.06, "it is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose.... [T]he idea of combining them flows logically from their having been individually taught in the prior art." *In re Kerkhoven*, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980).

CONCLUSION

Claims 3-14 are rejected.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SARA E. CLARK whose telephone number is (571) 270-7672. The examiner can normally be reached on Mon - Thu, 8:30 am - 5:00 pm (EST). If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brian-Yong Kwon, can be reached on 571-272-0581. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Brian-Yong S Kwon/
Supervisory Patent Examiner, Art Unit 1613

/SARA E. CLARK/
Examiner, Art Unit 1613